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CLINICAL REVIEW

Does obstructive sleep apnea cause endothelial dysfunction? A critical review of the literature

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SUMMARY

Endothelial dysfunction is characterized by impaired endothelium-dependent vasodilatation and is an independent predictor of adverse cardiovascular consequences. The ease with which endothelial function can be assessed has led to it becoming a useful marker of cardiovascular diseases in research studies. Obstructive sleep apnea (OSA) has been independently associated with endothelial dysfunction which may explain the increased risk for cardiovascular and all-cause mortality in this population. One possible mechanism for the development of endothelial dysfunction in OSA is through the cyclical pattern of hypoxia and re-oxygenation. This creates a haemostatic imbalance in which nitric oxide bio-availability is reduced and pro-inflammatory and pro-thrombotic forces prevail. Furthermore the repair capacity of the endothelium to protect itself against this increased damage is diminished. All of these pathways contribute to vascular disease which ultimately gives rise to adverse cardiovascular consequences.

This review aims to provide a critical appraisal of the cross-sectional and interventional studies which have investigated micro- and macro-vascular endothelial dysfunction in OSA with emphasis on randomised controlled studies.

Introduction

Obstructive sleep apnea (OSA) is a common condition which is characterised by repetitive occlusion to the upper airway during sleep. The link between OSA and cardiovascular disease (CVD) is becoming increasingly recognised. Several prospective community-based studies have reported an increased risk for all-cause and cardiovascular mortality in men with untreated severe OSA independent of traditional CVD risk factors [1–3]. Increased incident stroke [4,5], coronary heart disease [6] and heart failure [6] have also been shown in individuals with severe OSA. The increased risk for incident stroke and coronary heart disease has been confirmed in two recent meta-analyses [7,8], with the latter analysis also confirming an overall increase in risk in severe OSA compared to no OSA for all-cause mortality [8]. Even though the data from these cohort studies offer credible evidence of a causal association between OSA and CVD, randomised controlled trials assessing the effectiveness of continuous positive airway pressure (CPAP) to reduce these hard endpoints are not yet available. The requirement for long-term follow up in hard endpoint trials has resulted in the majority of research focussing on intermediate markers of CVD risk.

Endothelial dysfunction represents one of the earliest indicators of atherosclerosis development and is a predictive marker of future cardiovascular events [9–11]. Endothelial dysfunction has in particular been proposed as a key mechanism linking OSA with adverse cardiovascular consequences. The association between OSA and endothelial dysfunction is thought to be directly caused by recurrent hypoxia and re-oxygenation (intermittent hypoxia) that occurs as a result of recurrent apneas during sleep [12]. Pathways in which chronic intermittent hypoxia may negatively affect endothelial function include reduced endothelial nitric oxide bioavailability [13–18], increased oxidative stress [19,20], systemic

Abbreviations: AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; CVD, cardiovascular disease; EDV, endothelial-dependent vasodilatation; EIV, endothelial-independent vasodilatation; FMD, flow mediated dilatation; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; $TSaO_2 < 90\%$, sleep time spent with arterial oxyhaemoglobin saturation under 90%.

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inflammation [20] and sympathetic over-activity [21–23]. This impairment in endothelial function is accompanied by the promotion of circulating adhesion molecules [24,25], vascular damaging micro-particles [26,27] and hyper-coagulability [28,29]. Moreover the reduction of repair capacity through diminished numbers of circulating endothelial progenitor cells is another pathway in which endothelial dysfunction may occur in OSA [30]. Recently non alcoholic fatty liver disease has been suggested as a possible mechanism for the endothelial dysfunction in OSA [31]. This review will discuss in detail the current evidence of the causal association between OSA and endothelial dysfunction with emphasis on recent randomised controlled studies of CPAP treatment. Evidence will be presented separately for endothelial dysfunction in the micro- versus macro-vasculature. The underlying mechanisms linking OSA to endothelial dysfunction have been recently reviewed [32,33] and therefore will not be detailed here. A recent review has covered the non-invasive assessment of subclinical cardiovascular disease in OSA including studies investigating the association between OSA and endothelial function as measured by flow mediated-dilatation (FMD) [34]. The current review will provide more detailed information on the association between OSA and endothelial function. It will incorporate endothelial dependent and independent-vasodilation within both the macro and micro-vasculature. It will also include the results of CPAP intervention studies which were not described in the previous review.

Methods

An electronic search using PubMed database was conducted. We included literature published up to April 2014. The keywords utilised in the search were 'sleep apnea' with 'endothelial function' and then these terms combined with 'continuous positive airway pressure (CPAP)'. The search was limited to include full-text and English language publications. References of the selected studies were reviewed to identify additional relevant studies that were not found in the initial search. We specifically included all population-based studies ($n = 4$), case-controlled studies ($n = 40$) and interventional CPAP studies both observational ($n = 22$) and randomised ($n = 9$) which assessed a measurement of vascular reactivity. Cross-sectional studies that examined the effect of OSA on endothelial function with or without another condition (e.g., OSA + metabolic syndrome vs OSA − metabolic syndrome) were not included [31,35,36].

Endothelial dysfunction

The vascular endothelium is an active mono-layer of cells which line the internal vasculature. Endothelial cells produce nitric oxide, which protects vessels against atherosclerosis through the promotion of local vasodilatation and the inhibition of platelet aggregation, monocyte adhesion and vascular smooth muscle proliferation [37]. Endothelial dysfunction has therefore been implicated as one of the earliest detectable and possibly reversible abnormalities during atherosclerosis and the development of CVD. Endothelial dysfunction commonly refers directly to impaired endothelium-dependent vasodilatation (EDV) which is generally related to decreased nitric oxide bioavailability. In contrast, endothelium-independent vasodilatation (EIV) can also be assessed and generally represents further structural damage related to smooth muscle dysfunction in the arterial wall. Both EDV and EIV can be measured in either the macro- and micro-vasculature.

Endothelial function within the macro-vasculature can be assessed by several methods. FMD is the most common and measures change in the diameter of the brachial artery using non-invasive ultrasound, before and after ischaemia brought about by occluding blood flow to the arm. The subsequent reactive hyperaemia response, after the release of the cuff, stimulates endothelial nitric oxide release which causes vascular smooth muscle relaxation and dilatation [38,39]. Hand vein compliance is another technique which measures the maximum venodilation after the intra-venous administration of an endothelium-dependent vasodilator (e.g., bradykinin, or acetylcholine). EIV can be assessed using brachial artery ultrasound or hand vein compliance after the administration of an endothelium-independent vasodilator (e.g., nitroglycerin, a nitric oxide donor or sodium nitroprusside, a nitric oxide releasing drug). Studies have also implemented pulse wave analysis after inhaled salbutamol or sublingual nitroglycerin to assess endothelium dependent and independent responses respectively [40].

In contrast to the macro-vasculature, endothelial function within the micro-vasculature can be assessed by venous occlusion plethysmography of the forearm [41] or cutaneous blood flow by laser Doppler flowmetry [42]. Both methods can measure EDV by determining the response to an endothelium-dependent mediator including either reactive hyperaemia or the administration of acetylcholine either by direct infusion or by skin iontophoresis. EDV can also be measured using peripheral arterial tonometry, a non-invasive assessment that measures the changes of the pulse wave amplitude before and during reactive hyperaemia [37,39]. EIV can be examined using venous occlusion plethysmography or laser Doppler flowmetry to measure the response after the administration of nitro-glycerin.

Interestingly, several methods of macro- and micro-endothelial dysfunction measurement have been shown to be poorly correlated [43] which questions whether the predictive power of one is the same as the other. The Framingham Heart Study ($n = 1023$) reported that there was no association between assessments of macro- (FMD) and micro-vascular (peripheral arterial tonometry) function and that each measure had varying correlations with cardiovascular risk factors [44]. This suggests that the mechanisms which promote damage in the different vascular beds may vary between the macro- and micro-vasculature. Hence in this review we will differentiate between assessments of endothelial dysfunction in the macro- and micro-vascular beds.

Evidence linking OSA to macro-vascular endothelial dysfunction

Population and clinical cross-sectional studies

Nested-case controlled studies within population-based cohorts have reported OSA subjects to have impaired FMD compared to controls (apnea hypopnea index [AHI] < 5) [45,46]. The role of gender in these two studies was inconsistent. The first reported an association between male gender and FMD in uni-variate analyses but this was lost in multi-variate analyses and only AHI remained significant. On the other hand the second study reported female gender modulated the association between OSA and FMD. In all participants ($n = 193$) there was a significant association between increasing OSA severity and worsening FMD, however after stratification by sex the association remained only in women ($n = 111$) and therefore the study concluded that women may be more vulnerable to OSA related CVD than men [46]. In addition, the largest study to date, the Sleep Heart Health/Cardiovascular Health Study ($n = 1032$), showed dose-dependent associations between OSA severity (AHI and sleep time spent with arterial oxyhaemoglobin saturation under 90% [$TSaO_2 < 90\%$]) with a reduction of FMD after adjustment with age, gender and race [47]. This association however, was reduced and lost significance after body mass index was added into the model. Furthermore these findings were consistent in both men and women after stratification. In contrast the Framingham/Sleep Heart Health Study ($n = 682$) [48] showed no

adjusted association between FMD and OSA severity (both AHI and $TSaO_2 < 90\%$) which may have been due to the majority of participants having mild OSA (63% had an AHI between 5 and 15 events/hour) and therefore less likely to have any significant intermittent hypoxia, a key process mediating endothelial damage in OSA. Furthermore the authors speculated that the lack of association between FMD and OSA in their study compared to others could be due to variations in cuff placement which has been shown to influence the measurement [49]. Despite these inconsistencies in the reports from cross-sectional population-based studies the majority of studies support that endothelial function is impaired in OSA.

Table 1 shows the clinical observational case-controlled studies examining macro-vascular endothelial dysfunction, as measured by FMD, hand vein compliance, invasive coronary endothelial function or pulse wave analysis, in OSA patients compared to controls. Of the 29 identified studies, 23 have reported diminished EDV in OSA patients compared to healthy controls. Furthermore studies have shown OSA severity to be a predictor of endothelial damage independent of gender and obesity [50–55]. Many studies which did not find a difference had small sample sizes which may explain their inconsistent findings [56–58]. Many studies have established a 'pure' effect of OSA by excluding hypertension, hyperlipidaemia, diabetes, medications and chronic CVD. Other studies of a more typical OSA population that specifically recruited obese subjects and those with controlled cardiovascular morbidity also showed impaired endothelial function in OSA subjects compared to both lean [59,60] and obese healthy controls [60]. This again suggests that the increased endothelial dysfunction was due to the OSA and not obesity. Additionally a study showed the impairment associated with OSA to be equivalent to that in type II diabetes mellitus patients [60]. A limitation however is that none of these studies have controlled for central obesity which has been shown to be a stronger predictor of OSA than generalized obesity [61] and an important cardio-metabolic disease risk factor [62–64]. In terms of age, an interesting association was shown in one study that found AHI predicted FMD impairment in the younger (less than 50 y) but not the older participants which the authors suggested could be due to OSA providing a pre-ageing effect [60]. Similar associations have also been reported between age and minimum oxygen saturation [55]. Despite these findings, associations between OSA and endothelial dysfunction have been shown in older individuals but larger populations may be required to see these effects [47]. Furthermore, the impairment of endothelial dysfunction may occur early in the evolution of the OSA since non-obese children with OSA have been shown to have impaired endothelial function compared to matched controls [65,66].

Only a sub-set of the studies assessing the association of OSA and endothelial dysfunction have measured EIV – a measure of smooth muscle dilatation independent of the endothelium [39]: Table 1. Of the studies which performed ultrasound Doppler of the brachial artery, only one reported increased impairment in OSA patients compared to controls [67]. The remainder have all shown EIV is not altered in OSA patients. Consistently, OSA patients were also shown not to have impaired venodilation in response to sodium nitroprusside compared to controls using the hand vein compliance method [68–70]. Collectively, the evidence from case-controlled studies suggests that EIV in the macro-vasculature is not impaired in OSA. This might be because longer exposure may be required for smooth muscle remodelling to occur. Future studies could focus on whether OSA further contributes to impaired EIV, in individuals with established CVD.

CPAP interventional studies

Table 2 shows the 16 identified within person observational studies that have measured FMD (12 studies) or hand vein compliance (four studies) before and after CPAP treatment. Of these studies, all but two have shown a significant improvement after a range of 1 night–6 mo of CPAP use. The studies which did not show a change in FMD may have been due to a small sample size ($n < 15$) but in one study the change was close to statistical significance ($p = 0.06$) [51]. Some of these studies have only shown increases in FMD in those who adhered to CPAP (defined as >4 h/night) [53,71,72] whereas others have reported the improvement was independent of hours of CPAP use [73,74]. However not all studies have reported the dose–response relationship between endothelial function change and compliance. In studies where it was reported, reasons for the lack of a dose–response relationship include the exclusion of non-compliant patients in the analysis [75] and also the small sample size of many studies. Conversely, of the seven studies that have assessed EIV, all but one has shown no change after CPAP treatment. The one study that did show an improvement with CPAP was one of the longest in duration [67] however another of the same length did not find any changes [53].

Table 3 shows the six randomised controlled CPAP intervention studies linking OSA with macro-vascular endothelial dysfunction, five as assessed by FMD and one by pulse wave analysis after salbutamol inhalation. Of those that measured FMD, four were prospective studies that randomised CPAP naïve men to receive either therapeutic CPAP or a control (sham, standard care or no therapy) for 1–6 mo. Two reported a significant between group difference [52,76] whereas one reported a significant improvement in FMD with CPAP but not sham, however the between group difference was not reported and thus the effect cannot be accurately interpreted [77]. The final prospective study failed to show any change in FMD however this was the smallest in sample size ($n = 13$) [78]. The other study that measured FMD recruited current compliant CPAP users of greater than 1 y and randomised them to 2 wk of CPAP withdrawal (sham treatment) or continued CPAP treatment and reported a significant worsening of FMD with CPAP withdrawal [79]. In the final study, pulse wave analysis after inhaled salbutamol was not affected by CPAP in a randomised sham-controlled trial. There have been previous reports however, questioning the accuracy of assessing endothelial function using pulse wave analysis after inhaled salbutamol as used in this study [80]. On the other hand, EIV was shown not to be altered with CPAP in randomised controlled studies ranging from 2 wk to 3 mo in duration (Table 3).

Therefore the overall evidence supports that EDV at the macro-vascular level is impaired in patients with OSA and is reversed with CPAP treatment. Limitations to these current data include that only a limited number of studies utilised a sham control to maintain adequate blinding and minimise confounding. Furthermore the lack of dose response to CPAP also needs to be clarified. In contrast EIV does not appear to be diminished in OSA and is not affected by CPAP, however further studies are required of longer treatment duration and in at-risk populations such as in severe OSA.

Evidence linking OSA to endothelial dysfunction in the micro-vasculature

Population and clinical cross-sectional studies

The literature regarding micro-vascular endothelial dysfunction in OSA is more limited and less consistent than the data on its macro-vascular counterpart which may be because of the larger variety of methods in which endothelial function can be measured in the micro-vasculature. To date no population-based cohorts have examined the association between OSA and micro-vascular endothelial dysfunction. Table 1 shows the clinical observational case-controlled studies examining micro-vascular endothelial dysfunction, as measured by venous occlusion plethysmography, laser Doppler flowmetry and peripheral arterial tonometry in OSA patients compared to controls.

Table 1
Endothelial dysfunction in OSA.

First author, year of publication	OSA vs control *n*/sex, population	AHI (events/h)	Age (y)	BMI (kg/m^2)	EDV measure	EDV impaired in OSA vs controls?	EIV measure	EIV impaired?	Comments
Macro-vascular									
Bagai 2014 [58]	17 (6 M) OSA 17 (2 M) Controls All community	18.7 ± 25.5 0.84 ± 0.8**	49 ± 11 37 ± 12**	31.9 ± 5.1 31.6 ± 5.6[a]	FMD	N (NS)	ND		
Bayram 2009 [53]	29 M OSA 17 M Controls All sleep clinic	60.4 ± 22.1 2.5 ± 0.6	44 ± 8 43 ± 9[a]	30.2 ± 5.2 27.8 ± 4.0[a]	FMD	Y**	GTN-ID	N (NS)	**UCA:** EDV vs AHI ($r = -0.63$**). **MVA**: AHI** predicted EDV after adj age, BMI.
Blomster 2013 [102]	80 (60 M) OSA 45 (24 M) Habitual Snorer Controls All sleep clinic	9.3 ± 3.3 1.9 ± 1.4**	50 ± 9 46 ± 11*	32.5 ± 3.0 31.7 ± 3.7[a]	FMD	N (NS)	GTN-ID	N (NS)	
Brunetti 2013 [66]	23 (12 M) SDB 32 (14 M) controls Paediatric sleep clinic	NR	9 ± 3 10 ± 3[a]	19 ± 3 18 ± 3[a]	FMD	Y**	ND		**UCA:** EDV vs AHI in SDB group ($r = -0.56$**).
Bruno 2013 [103]	20 (18 M) OSA − CVD risk factors 20 (17 M) OSA + CVD risk factors 20 (15 M) All sleep clinic	35.2 ± 10.6 41.8 ± 20.4 3.5 ± 1.4*	53 ± 12 54 ± 13 51 ± 8*	26.4 ± 3.0 33.2 ± 4.7* 26.2 ± 3.6	FMD	Y* Y*	GTN-ID	N (NS)	**UCA:** EDV not with OSA severity.
Butt 2011 [67]	36 (26 M) OSA Sleep clinic 36 (24 M) controls community (AHI < 15) 36 (27 M) HT controls HT clinic	36 ± 20 vs 3 ± 1** 4 ± 2**	49 ± 10 47 ± 9[a] 48 ± 11[a]	32 ± 6 31 ± 6[a] 30 ± 5[a]	FMD	Y* N compared to OSA (NS)	GTN-ID	Y* N compared to OSA (NS)	WC OSA > Controls.
Cassar 2014 [104]	102 (36 M) OSA 41 (10 M) controls All sleep clinic	13 (8, 27) 2 (1, 3)**	50 ± 13 47 ± 9[a]	33.2 ± 6.9 32.3 ± 7.4[a]	Invasive Coronary EDV	N	ND		Retrospective study. EDV not associated with OSA severity.
Chung 2007 [105]	40 M severe 28 M mild/mod 22 M controls All sleep clinic	41.1 ± 18.2 11.2 ± 5.3 1.1 ± 0.8** (ODI)	43 ± 9 42 ± 10 42 ± 9[a]	26.6 ± 2.6 26.3 ± 4.1 26.2 ± 3.9[a]	FMD	Y* severe N (NS) mild/mod	ND		**UCA:** EDV vs AHI ($r = -0.31$**), ODI ($r = -0.35$**), meanSaO_2 ($r = 0.25$*), minSaO_2 ($r = 0.35$**), %$T < SaO_2$90 ($r = -0.41$**). **MVA:** ODI** predicted EDV after adj age, BMI, neck, waist/hip, SBP, DBP, AHI, $T < SaO_2$90%.
Chung 2010 [54]	44 M severe 39 M mild/mod 29 M controls All sleep clinic	56.8 ± 20.0 17.1 ± 6.9 3.2 ± 1.6**	44 ± 6 45 ± 9 44 ± 6[a]	27.9 ± 3.4 26.7 ± 2.7 27.2 ± 2.9[a]	FMD	Y* severe Y* mild/mod	ND		**UCA:** EDV vs AHI ($r = -0.32$**), ODI ($r = -0.31$**), meanSaO_2 ($r = 0.29$**), meanSaO_2 ($r = 0.30$**), %$T < SaO_2$90 ($r = -0.31$**). **MVA:** MinSaO_2** predicted EDV after adj. AHI, %T < $SaO_2$90, meanSaO_2, meanSaO_2, DBP SBP, BMI, neck, waist/hip, glucose.
Del Ben 2012 [106]	30 (25 M) severe 61 (43 M) mild/mod 47 (31 M) snorer controls All sleep clinic	42.8 ± 14.2 14.6 ± 8.0 1.2 ± 1.4**	57 ± 10 53 ± 12 51 ± 12[a]	32.8 ± 5.1 30.5 ± 4.5 29.3 ± 3.9**	FMD	Y* (Between all three groups)			**UCA:** EDV vs AHI significant negative association (statistics not reported). **MVA:** AHI did not predict EDV adj for confounders.
De la Pena 2008 [57]	13 M OSA 13 M controls All sleep clinic	49 ± 52 ± 1** NR	45 ± 3 45 ± 2[a]	28.4 ± 0.6 26.3 ± 0.8[a]	FMD	N (NS)	GTN-ID	N (NR)	
Duchna 2006 [70]	10 M mild OSA 10 M controls All NR	6.7 ± 3.8 2.8 ± 2.9**	51 ± 10 45 ± 8[a]	27.1 ± 2.9 7.5 ± 1.9[a]	HVC (BDK)	Y*	HVC (GTN-ID)	N (NR)	
Duchna 2005 [69]	16 M OSA 12 M controls All NR	22.4 ± 21.7 1.6 ± 1.1** (SEM)	50 ± 10 45 ± 9[a] (SEM)	27.7 ± 2.4 27.4 ± 1.2[a] (SEM)	HVC (BDK)	Y**	HVC (GTN-ID)	N (NS)	

Duchna 2000 [68]	12 M OSA sleep clinic 12 M controls NR	39.3 ± 31.4 ND	49 ± 9 46 ± 8[a]	29.8 ± 4.8 27.8 ± 1.7[a]	HVC (BDK)	Y**	HVC (GTN)	N (NS)	Responsiveness to BDK decreased with decreasing MinSaO_2 and increasing %T < 90SaO_2.
El Solh 2007 [107]	14 M OSA sleep clinic 10 M controls volunteers at wellness clinic	27.3 ± 12.5 3.9 ± 1.1**	46 ± 5 43 ± 7[a]	30.6 ± 4.7 27.8 ± 3.6[a]	FMD	Y*	ND		
Ip 2004 [52]	28 M OSA 12 M controls All sleep clinic	46.0 ± 14.5 2.4 ± 2.0	43 ± 9 41 ± 12	29.4 ± 5.5 27.7 ± 2.8	FMD	Y**	GTN-ID	N (NS)	**UCA:** EDV vs AHI (r = −0.66**), %T < $SaO_2$90 (r = −0.62**), minSaO_2 (r = 0.58**). **MVA:** AHI** predicted EDV after adj. age, BMI, DBP, smoking, cholesterol (same when AHI replaced with %T < $SaO_2$90** and minSaO_2**)
Jelic 2009 [51]	16 (11 M) OSA sleep clinic 16 (8 M) controls community	22 ± 24 0.1 ± 0.5**	36 ± 9 36 ± 11[a]	27 ± 2 26 ± 3[a]	FMD	Y**	ND		SBD excluded by PSG in controls. BMI > 30 excluded.
Jelic 2008 [71]	30 (20 M) OSA sleep clinic 15 (9 M) controls community	25 (10, 52) 0 (0, 0)**	38 ± 11 39 ± 7[a]	34 ± 8 30 ± 6[a]	FMD	Y**	ND		SDB excluded by PSG in controls. EDV negatively associated with tertiles of AHI, %T < $SaO_2$90, SaO_2 nadir and ODI4** after adj. age, sex, BMI.
Jones 2013 [108]	20 (13 M) OSA 20 (13 M) controls	32 (22, 41) 4 (3, 6) NR	44 ± 7 44 ± 7[a]	29.7 (27.4, 32.7) 29.4 (27.4, 33.5)[a]	PWA (inhaled Salbutamol)	Y*	PWA (GTN)	N	**UCA:** AHI not with EDV or EIV.
Kato 2000 [56]	8 M, NR 9 M, NR	52 ± 22 1 ± 0**	35 ± 3 30 ± 1[a]	44 ± 4 48 ± 3[a]	FMD	N (NS)	GTN-ID	N (NS)	
Kohler 2008 [109]	64 (57 M) OSA sleep clinic 15 (13M) controls GP database	23.1 ± 15.1 2.9 ± 1.1** (ODI)	58 ± 7 8 ± 7[a]	32.9 ± 6.2 31.7 ± 2.6[a]	FMD	Y**	GTN-ID	N (NS)	Aged 45–75 y. **UCA:** EDV not with ODI.
Namtvedt 2013 [45]	37 (26 M) OSA 34 (20 M) controls All community	19.1 (13.9, 28) 0.4 (0.1, 1.7)**	47 (42, 53) 43 (38, 49)*	30.1 ± 4.5 24.1 ± 1.9*	FMD	Y**	ND		**UCA:** EDV vs AHI (r = −0.33**), meanSaO [2] (r = 0.36**), SaO_2 nadir (r = 0.29*), BMI (r = −0.37**). **MVA:** AHI* predicted EDV after adj. male gender, DM, DBP, BBAD, BMI SubA: Obese vs lean: FMD NS
Oflaz 2006 [110]	23 (20 M) OSA sleep clinic 15 (12 M) controls medical staff	53.1 ± 20.3 3.8 ± 0.9**	48 ± 8 46 ± 8[a]	28.9 ± 2.2 27.9 ± 1.1[a]	FMD	Y AM** & PM**	ND		AM FMD lower than PM FMD in OSA and controls (both**).
Panoutsopoulos 2012 [75]	20 M OSA 18 M controls All sleep clinic	25.4 ± 15.1 2.7 ± 1.4**	54 ± 11 48 ± 8[a]	31.3 ± 2 30.0 ± 2.1[a]	FMD	Y**	ND		**UCA:** EDV vs AHI (r = −0.81**), DSI (r = −0.83**), %T < $SaO_2$90 (r = −0.82**). **MVA:** AHI** predicted EDV after adj. age, BMI (same when AHI replaced with %T < $SaO_2$90**).
Patt 2010 [74]	7 (5 M) OSA sleep clinics 7 (5 M) controls community or sleep clinic	35 ± 10 3 ± 1** (SEM)	39 ± 5 36 ± 2[a] (SEM)	35 ± 2 30 ± 2[a] (SEM)	FMD	Y*	ND		Difference* remained after adjustment of BMI, age and sex.
Tan 2014 [111]	37 (21 M) OSA (AHI ≥ 1) 13 (7 M) Controls	13.4 ± 12.6 0.4 ± 0.4*	7.7 ± 1.9 7.0 ± 1.7[a]	1.3 ± 1.0 1.5 ± 0.7[a] (BMI z scores)	FMD	N (NR)	ND		
Tanriverdi 2006 [50]	40 (32 M) OSA 24 (19 M) controls All sleep clinic	25.3 ± 11.4 3.0 ± 1.5**	51 ± 9 52 ± 5[a]	29.8 ± 5.3 29.4 ± 3.9[a]	FMD	Y**	GTN-ID	N (NS)	**UCA:** EDV vs RDI (r = −0.52**). No correlations with EIV. **MVA:** RDI, %T < $SaO_2$90 & age

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Table 1 (*continued*)

First author, year of publication	OSA vs control *n*/sex, population	AHI (events/h)	Age (y)	BMI (kg/m^2)	EDV measure	EDV impaired in OSA vs controls?	EIV measure	EIV impaired?	Comments
									predicted EDV after adj BMI % $T < SaO_2 90$ ($r = -0.62^{**}$).
Yim-Yeh 2010 [59]	38 (20 M) OSA 34 (9 M) controls Mainly community	23.3 (15.8, 40.0) 2.7 (1.3, 5.9)**	44 ± 10 32 ± 12**	37.3 (32.6, 45.3) 37.5 (33.4, 42.9)[a]	FMD	Y**	GTN-ID	N (NS)	Obese subjects (BMI > 30 kg/m^2). Gender did not affect EDV or EIV. **MVA**: Age* not OSA status predicted EDV after adj. BMI. **SubA:** FMD impaired in OSA subjects aged<50 y** but not subjects aged>50 y (NS).
Yim-Yeh 2011 [60]	38 (20 M) OSA 14 (3 M) Lean Controls 33 (9 M) Obese Controls All community 68 (37 M) DM, endocrine/podiatry clinic	23.3 (15.8, 40.0) ND NR ND	44 ± 10 59 ± 7 33 ± 12 58 ± 9	37 (33, 45) 23 (20, 27) 38 (34, 43) 34 (31, 39)	FMD	Y**lean Y**obese N (NR) DM	GTN-ID	N (NR) N (NR) Y compared to all groups**	Obese subjects (BMI > 30). OSA not excluded by PSG in lean controls/DM's. **MVA:** OSA status* predicted EDV after adj. DM, BBAD, obesity. **SubA:** MetS had no additional effect on FMD and NTG-ID in subjects with OSA.
Micro-vascular									
Buchner 2011 [82]	11 M OSA 8 M controls All sleep clinic	42.4 ± 20.2 1.4 ± 1.5**	51 ± 7 45 ± 11[a]	30.1 ± 6.6 25.6 ± 2.9[a]	VOP (ACH)	Y**	VOP (SNP)	N (NR)	**UCA:** EDV vs AHI ($r = -0.68^{**}$), meanSaO_2 ($r = 0.52^{*}$). Not with % $T < SaO_2 90$ or BMI. Infusion of Vitamin C acutely improved EDV in OSA patients. **MVA:** AHI & age predicted EDV after adj. BMI, HT, DM, HL, meanSaO_2 WC > in OSA.
Butt 2011 [67]	36 (26 M) OSA sleep clinic 36 (24 M) controls community 36 (27 M) HT controls HT clinic	36 ± 20 3 ± 1[a] 4 ± 2[a]	49 ± 10 47 ± 9[a] 48 ± 1[a]	32 ± 6 31 ± 6[a] 30 ± 5[a]	LDF-I (ACH)	Y** N (NS)	LDF-I (SNP)	Y ($p < 0.05$) N (NS)	No difference between OSA vs HT controls.
Carlson 1996 [88]	6 M, sleep clinic 6 M, controls	49 ± 9 ND	49 ± 4 (NT) 61 ± 3 (HT) Vs 51 ± 4 (NT) 49 ± 2 (HT)	28.6 ± 0.6 26.6 ± 0.8	VOP (ACH)	Y*	VOP (SNP)	Y (OSA + HT)	Normotensive (NT) and Hypertensive (HT) subgroup analysis HT did not influence difference in EDV between OSA & controls.
Cereda 2013 [112]	13 (11 M) mod/sev OSA AHI ≥ 20 24 (19 M) AHI < 20	29.3 ± 10.4 8.3 ± 6.3**	62 ± 7 60 ± 11[a]	28.4 ± 5.8 27.4 ± 4.9[a]	AM PAT	N (NS)	ND		All patients had a clinical diagnosis of acute ischemic event in the previous 60–90 days. **UCA:** EDV not with AHI. **MVA:** AHI did not predict EDV
Gozal 2007 [65]	26 (16 M) OSA 8 (5 M) controls Paediatric sleep clinic	11.9 ± 2.2 0.0 ± 0.0**	6.9 ± 0.6 6.8 ± 0.5[a]	17.1 ± 0.6 16.8 ± 0.5[a]	Cutaneous blood flow	Y**	ND		Non-obese OSA. **UCA:** EDV not with PSG measures.
Imadojemu 2002 [90]	8 (6 M) OSA sleep clinic 9 (7 M) controls community	47 ± 8 0.4 ± 0.2 (SEM)	52 ± 4 52 ± 5[a] (SEM)	40 ± 4 35 ± 3[a] (SEM)	VOP (hyperaemia)	Y*	ND		
Itzhaki 2005 [85]	19 (17 M) severe 27 (20 M) mild/mod 17 (11 M) controls All sleep clinic	41.7 ± 10.9 17.5 ± 5.7 6.7 ± 2.0	48 ± 11 46 ± 8 47 ± 7[a]	29.2 ± 3.4 29.2 ± 6.4 28.3 ± 3.8[a]	AM PAT	Y** N	ND		**UCA:** AHI vs AM PAT ($r = -0.42^{**}$) in all subjects. **MVA:** AHI** and Sleep Efficiency** predicted EDV.
Itzhaki 2005 [85]	13 (11 M) severe 15 (9 M) mild/mod 10 (6 M) controls All sleep clinic	40.5 ± 7.7 16.0 ± 4.6 7.1 ± 1.5	47 ± 10 45 ± 10 46 ± 7[a]	29.1 ± 3.5 30.5 ± 7.7 29.1 ± 3.5[a]	PM PAT ΔPAT%	N (NS) (Between all three groups) Y*	ND		Sub-set of above study. **UCA:** ΔPAT% or PM PAT not with AHI, minSaO_2. **MVA:** AHI predicted ΔPAT% after adj. sex, smoking. Sex & age

						(Between all three groups)			predicted PM PAT adj. for OSA status.
Jurado-Gamez 2011 [84]	46 (34 M) OSA 23 (15 M) controls All sleep clinic	49 ± 32.1 3 ± 0.9**	47 (40, 47) 48 (44, 51)[a]	31 (27, 34) 30 (28, 31)[a]	LDP (hyperaemia)	Y Post Sleep** N Pre Sleep (NS)	ND		**UCA:** EDV vs AHI ($r = -0.54^{**}$), ODI ($r = -0.57^{**}$) and meanSaO$_2$ ($r = 0.43^*$). Not with minSaO$_2$, arousal index. **MVA:** ODI* predicted EDV.
Kato 2000 [56]	8 M OSA 9 M controls All NR	52 ± 22 1 ± 0	44 ± 4 48 ± 3[a]	35 ± 3 30 ± 1[a]	VOP (ACH)	Y**	VOP (SNP)	N (NS)	**UCA:** EDV not with AHI or MinSaO$_2$.
Kheirandish-Gozal 2010 [113]	80 (48 M) OSA 20 (11 M) controls Paediatric sleep clinic	12.9 ± 8.5 0.4 ± 0.3**	7.2 ± 1.4 7.1 ± 1.6[a]	0.96 ± 0.3 0.56 ± 0.2 (z-score)*	Cutaneous blood flow	N Magnitude of peak flow Y TMAX**	ND		PSG measures not correlated with EDV.
Kraiczi 2000 [87]	10 M OSA 10 M controls All paper advert	39.8 ± 22.6 1.6 ± 1.9	53 ± 11 53 ± 12[a]	28.4 ± 3.1 27.6 ± 2.4[a]	VOP (ACH)	N (NS)	ND		
Trzepizur 2009 [83]	12 M controls 9 M controls All sleep clinic	32 (24, 51) 6 (4, 11)	46 (43, 49) 42 (43, 49)	26.8 (24.8, 30.3) 27.4 (24.5, 29.2)	LDF-I (ACH)	Y*	LDF (SNP)	N (NR)	**UCA:** EDV vs AHI ($r = -0.49^*$), ODI3 ($r = -0.63^{**}$). OSA severity not with EIV.

Data are mean ± standard deviation or median (25th, 75th inter-quartile range) except if otherwise stated. * denotes $p < 0.05$ and ** $p < 0.01$. If p values are not stated then they were not reported.
ACH = acetylcholine, adj = adjustment for by, AHI = apnea hypopnea index, AM = morning, BBAD = basal brachial artery diameter, BDK = bradykinin induced dilatation, BMI = body mass index, DM = diabetes mellitus, DBP = diastolic blood pressure, EDV = endothelium-dependent vasodilatation, EIV = endothelium-independent vasodilatation, FMD = flow mediated dilatation, GP = general practice, GTN-ID = nitro-glycerine induced dilatation, HVC = hand vein compliance, HT = hypertension, HL = hyperlipidemia, IQR = inter-quartile range, LDP = laser Doppler periflux, LDF-I = laser Doppler flowmetry after iontophoresis, M = males, MeanSaO$_2$ = mean nocturnal oxygen desaturation levels, MetS = metabolic syndrome, MinSaO$_2$ = nocturnal minimum oxygen desaturation levels, MVA = multiple variable analysis, N = no, ND = not done, NR = not reported, NS = not significant, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, PSG = polysomnography, PAT = reactive hyperaemia peripheral arterial tonometry, PM = evening, PWA = pulse wave analysis, RDI = respiratory disturbance index, SBP = systolic blood pressure, SDB = sleep disordered breathing, SEM = standard error of the mean, SNP = sodium nitroprusside, SubA = sub-analysis, SubP = substance p, TMAX = max velocity during 1st 10 s after cuff deflation/corresponding rest velocity, %$T <$ SaO$_2$90 = percent time oxygen saturation spent below 90%, UCA = univariate correlational analysis, VOP = venous occlusion plethysomography, vs = versus, WC = waist circumference, Y = yes.
[a] Denotes no differences compared to OSA patients.

Of the 14 identified studies, all but three have shown OSA subjects to have impaired micro-vascular EDV compared to healthy controls. The impairment has also been shown to be correlated with OSA severity [81–86]. Interestingly the authors of the study that failed to show venous occlusion plethysmography impairment in OSA patients [87] had previously reported a difference in a separate group of patients [88]. The authors suggested a stricter inclusion and more thoroughly matched controls in one of the studies may have led to the discrepancies in their findings. Furthermore slightly differing methodologies (measuring flow conductance versus resistance) in the two studies may have led to the conflicting findings. Two other studies, both from the same research group, showed no difference in laser Doppler flowmetry response to skin iontophoresis of acetylcholine between obese OSA patients and either non-obese or obese controls [59,60]. The authors suggested this was due to incomplete matching between cases and controls. Interestingly both of these studies showed a between-group difference in FMD [59,60] which in one of the studies led the authors to conclude that OSA impairs macro-vascular EDV but not skin microcirculatory function [59]. This however is not supported by the majority of studies which have reported that OSA is associated with impaired micro-vascular endothelium function, including studies which have also measured skin microcirculatory function (Table 1).

A paradoxical finding from a recent large clinical cohort of men with both CVD and OSA (AHI 15–50 events/h, $n = 267$) was a negative linear association between oxygen desaturation index (ODI) and endothelial dysfunction in those with an ODI below 24.6 events/h [86]. Thus in OSA patients with mild to moderate intermittent hypoxia, the higher the ODI, the better their endothelial function. This finding is consistent with the hypothesis that mild-moderate OSA may be protective against CVD [89]. However in those patients with an ODI above 24.6 events/h the association was as expected i.e., as the ODI increased so did the endothelial dysfunction.

In line with the studies on the macro-vasculature, the majority of case-controlled studies at the micro-vascular level have also not reported any impairment in EIV in OSA patients compared to controls (Table 1). Only two studies have reported EIV to be impaired in OSA patients compared to healthy controls [88]. Interestingly, in one of these studies, the difference was not seen when OSA patients were compared to hypertensive controls which could indicate similar damage in these two patient groups who are at increased risk of CVD. The investigators excluded pre-existing conditions including hypertension, hyperlipidaemia and diabetes and matched patients to controls in an attempt to eliminate confounding but this limited the sample size ($n = 8$ in each group) [88]. As previously discussed, the second study showed an impairment in EIV in OSA patients compared to controls in both the micro- and macro-vasculature [67]. The severity of the OSA in these patients was not worse than in the other studies and investigators specifically excluded confounding conditions such as hypertension, hyperlipidaemia and diabetes. Another study showed that subjects with severe OSA, as defined by an ODI above 20 events/h, had impaired EIV compared to those with an ODI below 20 events/h [81] indicating that smooth muscle function may be directly related to the frequency of hypoxic insult. This finding however has not been demonstrated in other protocols that have failed to correlate EIV impairment with OSA severity [59,83]. The studies performed to date however have all been relatively small and thus these discrepancies need to be addressed in larger studies. Therefore overall the evidence from cross-sectional data and clinical case-controlled studies supports that EDV but not EIV at the micro-vascular level is impaired in patients with OSA compared to controls.

CPAP interventional studies

Table 2 shows the eight identified within person observational studies that have measured micro-vascular EDV before and after

Table 2
Before and after studies of the effect of CPAP on endothelial dysfunction.

First author, year of publication	n/sex	Age (y)	AHI (events/h)	Duration	EDV technique	CPAP change in EDV	EIV technique	CPAP change in EIV	Comments
Macro-vascular									
Bakker 2013 [92]	15 (11 M)	48 (range 26–60)	36.5 (24.7, 77.3)	6 mo	FMD	↔ (NS)	GTN-ID	↔ (NS)	
Bayram 2009 [53]	29 M	44 ± 8	60.4 ± 22.1	6 mo	FMD	↑ CPAP users** ↔ CPAP failures (NS)	GTN-ID	↔	ΔFMD correlated with CPAP use ($r = 0.76$**)
Butt 2011 [67]	36 (26 M)	49 ± 10	36 ± 20	26 wk	FMD	↑**	GTN-ID	↑**	
Del Ben 2012 [106]	10 M	NR	43.4 ± 12.6	6 mo	FMD	↑*	ND		
Duchna 2006 [70]	7 M	51 ± 10	6.7 ± 3.8	161 ± 82 nights	HVC (BDK)	↑**	HVC (GTN)	↔	
Duchna 2005 [69]	16 M	50 ± 10	22.4 ± 21.7	6 mo	HVC (BDK)	↑**	HVC (GTN)	↔	
Duchna 2000 [68]	6 M	49	39.3 ± 31.4	8 wk	HVC (BDK)	↑**	HVC (GTN)	↔	
El Solh 2007 [107]	14 M	46 ± 5	27.3 ± 12.5	8 wk	FMD	↑**	ND		
Jelic 2008 [71]	22 (NR)	38 ± 11	25 (10, 52)	4 wk	FMD	↑ CPAP adherers** ↔ Non-adherers nor decliners ($p = 0.06$)	ND		CPAP adherers: ≥4 h/night
Jelic 2009 [51]	16 (9 M)	36 ± 9	22 ± 24	4 wk	FMD	↔ CPAP adherers ($p = 0.06$) ↔ Non-adherers nor decliners	ND		CPAP adherers: ≥4 h/night
Jelic 2010 [72]	26 (NR)	NR	NR	4 wk	FMD	↑ CPAP adherers* ↔ Non-adherers nor decliners (NS)			CPAP adherers: ≥4 h/night
Panoutsopoulos 2012 [75]	20 M	54 ± 11	25.4 ± 15.1	12 wk	FMD	↑**	ND		six CPAP failures not included in analysis
Patt 2010 [74]	7 (5 M)	39 ± 5	35 ± 10 (SEM)	12 wk	FMD	↑*	ND		ΔFMD not correlated with AHI or CPAP use.
Ohike 2005 [114]	10 M	53 ± 11	33 ± 14.7	4 wk	FMD	↑** at 1 & 4 wk	GTN-ID	↔	
Tulmac 2012 [115]	30 (22 M)	52 ± 11	60.6 ± 24.9	1 night	FMD	↑**	ND		Sub-analysis: only men, non-DM, non-HT & non-HL
Micro–vascular									
Bakker 2013 [92]	15 (11 M)	48 (range 26–60)	36.5 (24.7, 77.3)	6 mo	LDF-I (ACH)	↑*	LDF-I (SNP)	↔	
Oyama 2012 [91]	32 (19 M) OSA and MetS	54 ± 9	56.2 ± 21.6	12 wk	VOP (hyperaemia)	↑**	ND		UCA: EDV with AHI ($r = 0.57$**)
Buchner 2011 [82]	6 M	NR	37.9 ± 26.1	6 mo	VOP (ACH)	↑ (NS)	VOP (SNP)	↔	NR
Butt 2011 [67]	36 (26 M)	49 ± 10	36 ± 20	26 wk	LDF-I (ACH)	↑**	LDF-I (SNP)	↑*	
Imadojemu 2002 [90]	7 (6 M)	52 ± 4 (SEM)	47 ± 2 1.2	4.5 mo	VOP (hyperaemia)	↑*	ND		NR
Jurado-Gamez 2011 [84]	25 (NR)	47 (40, 47)	71 (52, 85)	12 wk	Cutaneous perfusion	↑**	ND		UCA: EDV with AHI ($r = 0.41$*), ODI ($r = 0.48$*) not with %T < $SaO_2$90
Lattimore 2006 [73]	10 (9 M)	49 ± 8 (SEM)	39 (15, 104)	12 wk	VOP (ACH)	↑**	VOP (SNP)	↔	Not severity of hypoxemia, AHI or CPAP use
Shiina 2010 [93]	50 (45 M)	54 ± 10	53.6 ± 22.1	12 wk	VOP (hyperaemia)	↔	ND		

Data are mean ± standard deviation or median (25th, 75th percentile). ↑ denotes an improvement and ↔ no change, * denotes $p < 0.05$ and ** $p < 0.01$.
ACH = acetylcholine, AHI = apnea hypopnea index, BDK = bradykinin, CPAP = continuous positive airway pressure, DM = diabetes mellitus, EDV = endothelium-dependent vasodilatation, EIV = endothelium-independent vasodilatation, FMD = flow mediated dilatation, GTN-ID = nitro-glycerine induced dilatation, HL = hyperlipidemia, HT = hypertension, HVC = hand vein compliance, LDF-I = laser Doppler flowmetry after iontophoresis, ND = not done, NR = not reported, ODI = oxygen desaturation index, ODI4 = number of oxygen desaturation index per hour below 4%, %T < $SaO_2$90 = the time spent below 90% of oxygen saturation, SEM = standard error of the mean, SNP = sodium nitroprusside, UCA = univariate correlational analysis, VOP = strain gauge venous occlusion plethysomography.

CPAP treatment. Most [67,73,82,84,90–92], but not all [93] have shown significant improvements in micro-vascular endothelial function after 3–6 mo of CPAP treatment. One study showed a non-significant increase after CPAP which was most likely due to a lack of power ($n = 6$) [82]. Only three of these studies have assessed EIV and two have reported no changes with CPAP treatment. As previously discussed the study that did show an improvement with CPAP also showed an improvement in macro-vascular EIV [67]. This study was of longer duration than the other studies which may explain the improvement that was seen (Table 2).

Table 3 shows the three identified randomised-controlled CPAP interventional studies linking OSA with micro-vascular endothelial dysfunction. Two of these studies have prospectively randomised moderate to severe patients to either sham or CPAP for 6 wk in a cross-over design [81] and for 12 wk in a parallel design [94]. The 6 wk study reported improved EDV and EIV as measured by venous occlusion plethysmography with CPAP whereas the 12 wk study showed no changes in peripheral arterial tonometry determined EDV. Conflicting results may be due to differences in the methods used to assess endothelial function. In addition, the former positive study specifically selected moderate to severe hypoxic OSA subjects (ODI4 > 20/h and mean AHI = 63 events/h) [81] whilst the latter study included generally less severe OSA (mean AHI = 37 events/h) [94]. Thus differences in OSA severity

Table 3
Randomised controlled trials of the effect of CPAP on endothelial dysfunction.

First author, year of publication	n/sex	Age (y)	AHI (events/h)	Duration and design	EDV technique	EDV CPAP vs controls	EIV technique	EDV improved between groups?
Macro-vascular								
Comondore 2009 [78]	13 (9 M) CPAP No Therapy	56 ± 8	27.9 (AHI ≥ 15).	4 wk, CO	FMD	NR FMD/GTN-ID ↔ (NS)	GTN-ID	NR
Ip 2004 [52]	CPAP (14, 14 M) No Therapy (13, 13 M)	44 ± 7 41 ± 11	47.7 ± 15.3 45.1 ± 14.3 (AHI ≥ 15).	4 wk, parallel	FMD	↑**	GTN-ID	↔ (NS)
Jones 2013 [116]	43 (28 M) CPAP Sham	46 ± 9	31 (20, 41)	12 wk, CO	PWA (Salbutamol inhalation)	↔ (NS)	GTN-ID	↔ (NS)
Kohler 2013 [76]	CPAP (107, 90 M) Standard Care (101, 87 M)	58.4 (7.2) 58.2 (7.5)	9.5 (3.8, 17.2) 10.4 (5.7, 16)	6 mo, parallel	FMD	↑**	GTN-ID	N (NS)
Kohler 2011 [79]	CPAP (20, 19 M) Sham (21, 21 M)	64 ± 5 62 ± 8	36 ± 17.3 45.3 ± 22.3 (Group ODI4 ≥ 10 events/h)	2 wk withdrawal, parallel	FMD	↓**	GTN-ID	↔ (NS)
Nguyen 2010 [77]	CPAP (10, 8 M) Sham (10, 10 M)	53 ± 12 54 ± 11	38.8 ± 21.4 31.6 ± 11.1 (RDI ≥ 15/h and ESS > 10).	3 mo, parallel	FMD	NR, (CPAP ↑*, Sham ↔ NS from baseline)	GTN-ID	NR (CPAP ↔, Sham ↔ from baseline)
Micro-vascular								
Cross 2008 [81]	27 (26 M) CPAP Sham	48 ± 2	63 ± 5 (AHI > 15, ODI4 > 20 events/h, ESS > 10).	6 wk, CO	VOP (ACH and SubP)	↑**	VOP (SNP)	↑**
Simpson 2013 [94]	CPAP (18 M) Sham (12 M)	52 ± 12 46 ± 11	38.1 ± 15.4 37.3 ± 18.2 (AHI ≥ 20 and ODI3 ≥ 15 events/h)	12 wk, parallel	PAT	↔ (NS)	ND	
Trzepizur 2009 [83]	12 M CPAP MAS (AHI ≥ 15 events/h)	56 (56, 58)	40 (31, 49)	2 mo, CO	LDF-I (ACH)	NR (CPAP ↑*, MAS↑*)	LDF-I (SNP)	NR (CPAP ↔, MAS ↔)

Data are mean ± standard deviation or median (25th, 75th percentile). ↑ denotes an improvement, ↔ denotes no change, ↓ denotes a worsening, * denotes $p < 0.05$ and ** $p < 0.01$.
AHI = apnea hypopnea index, ACH = acetylcholine, CO = cross-over, CPAP = continuous positive airway pressure, EDV = endothelial dependent vasodilatation, EIV = endothelial-independent vasodilatation, ESS = Epworth sleepiness scale, FMD = flow mediated dilatation, GTN-ID = nitro-glycerine induced dilatation LDF-I = laser Doppler flowmetry after iontophoresis, M = men, MAS = mandibular advancement splint,, ND = not done, NR = not reported, NS = not significant, ODI = oxygen desaturation index, ODI3 = number of oxygen desaturation index per hour >3%, ODI4 = number of oxygen desaturation index per hour >4%, PAT = reactive hyperaemia peripheral arterial tonometry, PWA = pulse wave analysis, RDI = respiratory disturbance index, SNP = sodium nitroprusside, SubP = substance *p*, VOP = venous occlusion plethysomography.

between the studies may explain the conflicting results. The final study compared CPAP to a mandibular advancement device and showed improvement with both devices but did not report the between-group difference. Furthermore no change in EIV was shown in this study [83].

Summary of vascular endothelial dysfunction in OSA

In summary, cross-sectional data of population-based studies suggest an association between OSA severity and impaired endothelial function however not all studies confirm this finding independent of other risk factors. However whether gender modulates EDV dysfunction needs to be examined further. In contrast, clinical based studies have repeatedly shown blunted EDV of both the macro- and micro-vasculature in OSA patients compared to controls. A major limitation of this evidence is that obesity has only been accounted for in some studies and this has nearly always been measured by body mass index which represents generalised obesity. Visceral abdominal fat is a stronger predictor of OSA than generalised obesity [61]. Visceral fat accumulation is greater in OSA patients than body mass index-matched controls [61,95,96] and has been shown to be an important predictor of CVD, beyond that of generalised obesity [97,98]. Furthermore visceral abdominal fat is an independent predictor of EDV [99–101]. Thus it is important to control for this factor in cross-sectional and longitudinal studies even by using a surrogate measure such as waist circumference. Alternatively, randomised controlled treatment studies automatically adjust for this bias and therefore provide plausible evidence that OSA alleviation can repair the endothelium and improve EDV, particularly in the macro-vascular beds. The improvement seen in the micro-vascular beds may only occur in subjects with severe sleep apnea who have concomitant hypoxia. However this needs to be reproduced in further randomised controlled studies. In contrast endothelium-independent dysfunction is not commonly shown in OSA patients compared to controls, suggesting that vascular smooth muscle remodelling may well take years to develop. The beneficial effect of CPAP may also require a longer time to be revealed than is feasible in a sham-controlled randomised study. However very severe OSA populations should be targeted first since this group will benefit most. Overall, the data included in this review suggests that endothelial dysfunction is an established risk factor for CVD and is associated with OSA. There is mounting evidence suggesting that the association between OSA and endothelial dysfunction is causal; however more long-term randomised controlled trials are needed to confirm this.

Practice Points

- Endothelial dysfunction is an established independent risk factor for cardiovascular disease. Many of the factors that link endothelial dysfunction to cardiovascular disease occur in obstructive sleep apnea.
- The hypoxia/re-oxygenation cyclical pattern that occurs at night in obstructive sleep apnea patients is a key process for the development of endothelial dysfunction in obstructive sleep apnea. This cyclical pattern triggers several harmful processes which promote the destruction of the endothelium as well as reduce its capacity for repair.
- Cross-sectional analyses of population-based studies and case-controlled studies have consistently shown an association between obstructive sleep apnea and endothelial-dependent vasodilatation. Although more research has used techniques of macro-vascular endothelial function assessment, the evidence suggests the association occurs at both the macro- and micro-vascular levels. Controlling for potential confounders has occurred in some studies through adjustment or matching of controls. Studies have repeatedly used body mass index as a surrogate marker of obesity which does not adequately represent central obesity, in particular visceral abdominal fat, which is more closely related to obstructive sleep apnea and increased cardiovascular disease risk.
- Randomised controlled studies generally show that continuous positive airway pressure improves macro-vascular endothelium-dependent function (flow mediated dilatation). On the other hand the evidence that continuous positive airway pressure improves micro-vascular endothelial-dependent vasodilatation is still unclear.
- Generally endothelial-independent vasodilatation does not appear to be impaired in obstructive sleep apnea or reversed after continuous positive airway pressure treatment. The impairment however may be related to the severity of intermittent hypoxia and may be reversed by continuous positive airway pressure in those patients with concurrent hypoxia.
- It is not known whether improved endothelial function with continuous positive airway pressure decreases hard cardiovascular endpoints.

Research agenda

- Larger controlled studies examining the efficacy of continuous positive airway pressure on endothelial dysfunction, specifically using techniques to assess micro-vascular endothelial-dependent vasodilatation are required.
- The effect of continuous positive airway pressure on endothelial-independent vasodilatation needs to be investigated in larger and longer randomised controlled studies. Future studies could recruit participants with severe obstructive sleep apnea or those with co-existing cardiovascular disease and obstructive sleep apnea as these individuals are more likely to have endothelial dysfunction and be at greater risk for cardiovascular disease.
- Future studies investigating the effect continuous positive airway pressure on hard cardiovascular outcomes are required.

Conflicts of interests

None to declare.

References

[1] Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton health study. Sleep 2008;31:1079–85.
[2] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071–8.
[3] Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009;6:e1000132.
[4] Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182:269–77.
[5] Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 2006;37:2317–21.
[6] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 2010;122:352–60.
[7] William LBJ, Loke Y, Kwok CS, Niruban A, Myint P. Association of obstructive sleep apnoea (OSA) with incident stroke: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatr 2013;84:e2.
[8] Wang X, Ouyang Y, Wang Z, Zhao G, Liu L, Bi Y. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. Int J Cardiol 2013;169(3):207–14.
[9] Poredos P. Endothelial dysfunction in the pathogenesis of atherosclerosis. Clin Appl Thromb Hemost 2001;7:276–80.
*[10] Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular health study. Circulation 2007;115:2390–7.
[11] Rossi R, Nuzzo A, Origliani G, Modena MG. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. J Am Coll Cardiol 2008;51:997–1002.
[12] Foster GE, Poulin MJ, Hanly PJ. Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. Exp Physiol 2007;92:51–65.
[13] Alonso-Fernandez A, Garcia-Rio F, Arias MA, Hernanz A, de la Pena M, Pierola J, et al. Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial. Thorax 2009;64:581–6.
[14] Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, et al. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med 2000;162:2166–71.
[15] Schulz R, Schmidt D, Blum A, Lopes-Ribeiro X, Lucke C, Mayer K, et al. Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy. Thorax 2000;55:1046–51.
[16] Noda A, Nakata S, Koike Y, Miyata S, Kitaichi K, Nishizawa T, et al. Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. Hypertens Res 2007;30:669–76.
[17] Ozkan Y, Firat H, Simsek B, Torun M, Yardim-Akaydin S. Circulating nitric oxide (NO), asymmetric dimethylarginine (ADMA), homocysteine, and oxidative status in obstructive sleep apnea-hypopnea syndrome (OSAHS). Sleep Breath 2008;12:149–54.
[18] Lavie L, Hefetz A, Luboshitzky R, Lavie P. Plasma levels of nitric oxide and L-arginine in sleep apnea patients: effects of nCPAP treatment. J Mol Neurosci 2003;21:57–63.
[19] Lavie L. Obstructive sleep apnoea syndrome—an oxidative stress disorder. Sleep Med Rev 2003;7:35–51.
[20] Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. Am J Respir Crit Care Med 2008;177:369–75.
[21] Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897–904.
[22] Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L. Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. J Appl Physiol 1995;79:581–8.
[23] Hijmering ML, Stroes ES, Olijhoek J, Hutten BA, Blankestijn PJ, Rabelink TJ. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. J Am Coll Cardiol 2002;39:683–8.
[24] Zamarron-Sanz C, Ricoy-Galbaldon J, Gude-Sampedro F, Riveiro-Riveiro A. Plasma levels of vascular endothelial markers in obstructive sleep apnea. Arch Med Res 2006;37:552–5.

* The most important references are denoted by an asterisk.

[25] Ohga E, Nagase T, Tomita T, Teramoto S, Matsuse T, Katayama H, et al. Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. J Appl Physiol 1999;87:10–4.
[26] Ayers L, Stoewhas AC, Ferry B, Stradling J, Kohler M. Elevated levels of endothelial cell-derived microparticles following short-term withdrawal of continuous positive airway pressure in patients with obstructive sleep apnea: data from a randomized controlled trial. Respiration 2013;85: 478–85.
[27] Priou P, Gagnadoux F, Tesse A, Mastronardi ML, Agouni A, Meslier N, et al. Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. Am J Pathol 2010;177:974–83.
[28] Phillips CL, McEwen BJ, Morel-Kopp MC, Yee BJ, Sullivan DR, Ward CM, et al. Effects of continuous positive airway pressure on coagulability in obstructive sleep apnoea: a randomised, placebo-controlled crossover study. Thorax 2012;67:639–44.
[29] Mehra R, Xu F, Babineau DC, Tracy RP, Jenny NS, Patel SR, et al. Sleep-disordered breathing and prothrombotic biomarkers: cross-sectional results of the Cleveland family study. Am J Respir Crit Care Med 2010;182: 826–33.
[30] Berger S, Lavie L. Endothelial progenitor cells in cardiovascular disease and hypoxia—potential implications to obstructive sleep apnea. Transl Res 2011;158:1–13.
[31] Minville C, Hilleret MN, Tamisier R, Aron-Wisnewsky J, Clement K, Trocme C, et al. Nonalcoholic fatty liver disease, nocturnal hypoxia, and endothelial function in patients with sleep apnea. Chest 2014;145: 525–33.
[32] Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 2010;7:677–85.
[33] Feng J, Zhang D, Chen B. Endothelial mechanisms of endothelial dysfunction in patients with obstructive sleep apnea. Sleep Breath 2012;16:283–94.
[34] Ali SS, Oni ET, Warraich HJ, Blaha MJ, Blumenthal RS, Karim A, et al. Systematic review on noninvasive assessment of subclinical cardiovascular disease in obstructive sleep apnea: new kid on the block! Sleep Med Rev 2014;18:379–91. pii: S1087-0792(14)00014-8. http://dx.doi.org/10.1016/j.smrv.2014.01.004.
[35] Amra B, Karbasi E, Hashemi M, Hoffmann-Castendiek B, Golshan M. Endothelial dysfunction in patients with obstructive sleep apnoea independent of metabolic syndrome. Ann Acad Med Singap 2009;38: 461–4.
[36] Akishita M, Ohike Y, Yamaguchi Y, Iijima K, Eto M, Ouchi Y. Obstructive sleep apnea exacerbates endothelial dysfunction in people with metabolic syndrome. J Am Geriatr Soc 2011;59:1565–6.
[37] Celermajer DS. Reliable endothelial function testing: at our fingertips? Circulation 2008;117:2428–30.
[38] Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111–5.
[39] Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–65.
[40] Wilkinson IB, Hall IR, MacCallum H, Mackenzie IS, McEniery CM, van der Arend BJ, et al. Pulse-wave analysis: clinical evaluation of a noninvasive, widely applicable method for assessing endothelial function. Arterioscler Thromb Vasc Biol 2002;22:147–52.
[41] Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. Br J Clin Pharmacol 2001;52:631–46.
[42] Turner J, Belch JJ, Khan F. Current concepts in assessment of microvascular endothelial function using laser Doppler imaging and iontophoresis. Trends Cardiovasc Med 2008;18:109–16.
[43] Gori T, Di Stolfo G, Sicuro S, Dragoni S, Lisi M, Parker JD, et al. Correlation analysis between different parameters of conduit artery and microvascular vasodilation. Clin Hemorheol Microcirc 2006;35:509–15.
[44] Hamburg NM, Palmisano J, Larson MG, Sullivan LM, Lehman BT, Vasan RS, et al. Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. Hypertension 2011;57:390–6.
[45] Namtvedt SK, Hisdal J, Randby A, Agewall S, Stranden E, Somers VK, et al. Impaired endothelial function in persons with obstructive sleep apnoea: impact of obesity. Heart 2013;99:30–4.
[46] Faulx MD, Larkin EK, Hoit BD, Aylor JE, Wright AT, Redline S. Sex influences endothelial function in sleep-disordered breathing. Sleep 2004;27:1113–20.
*[47] Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. Am J Respir Crit Care Med 2004;169:354–60.
*[48] Chami HA, Keyes MJ, Vita JA, Mitchell GF, Larson MG, Fan S, et al. Brachial artery diameter, blood flow and flow-mediated dilation in sleep-disordered breathing. Vasc Med 2009;14:351–60.
[49] Mannion TC, Vita JA, Keaney Jr JF, Benjamin EJ, Hunter L, Polak JF. Non-invasive assessment of brachial artery endothelial vasomotor function: the effect of cuff position on level of discomfort and vasomotor responses. Vasc Med 1998;3:263–7.
[50] Tanriverdi H, Evrengul H, Kara CO, Kuru O, Tanriverdi S, Ozkurt S, et al. Aortic stiffness, flow-mediated dilatation and carotid intima-media thickness in obstructive sleep apnea: non-invasive indicators of atherosclerosis. Respiration 2006;73:741–50.
[51] Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor P, et al. Endothelial repair capacity and apoptosis are inversely related in obstructive sleep apnea. Vasc Health Risk Manag 2009;5:909–20.
*[52] Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med 2004;169:348–53.
[53] Bayram NA, Ciftci B, Keles T, Durmaz T, Turhan S, Bozkurt E, et al. Endothelial function in normotensive men with obstructive sleep apnea before and 6 months after CPAP treatment. Sleep 2009;32:1257–63.
[54] Chung S, Yoon IY, Lee CH, Kim JW. The association of nocturnal hypoxemia with arterial stiffness and endothelial dysfunction in male patients with obstructive sleep apnea syndrome. Respiration 2010;79:363–9.
[55] Chung S, Yoon IY, Shin YK, Lee CH, Kim JW, Ahn HJ. Endothelial dysfunction and inflammatory reactions of elderly and middle-aged men with obstructive sleep apnea syndrome. Sleep Breath 2009;13:11–7.
[56] Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, et al. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 2000;102:2607–10.
[57] de la Pena M, Barcelo A, Barbe F, Pierola J, Pons J, Rimbau E, et al. Endothelial function and circulating endothelial progenitor cells in patients with sleep apnea syndrome. Respiration 2008;76:28–32.
[58] Bagai K, Muldowney 3rd JA, Song Y, Wang L, Bagai J, Artibee KJ, et al. Circadian variability of fibrinolytic markers and endothelial function in patients with obstructive sleep apnea. Sleep 2014;37:359–67.
[59] Yim-Yeh S, Rahangdale S, Nguyen AT, Jordan AS, Novack V, Veves A, et al. Obstructive sleep apnea and aging effects on macrovascular and microcirculatory function. Sleep 2010;33:1177–83.
[60] Yim-Yeh S, Rahangdale S, Nguyen AT, Stevenson KE, Novack V, Veves A, et al. Vascular dysfunction in obstructive sleep apnea and type 2 diabetes mellitus. Obesity 2011;19:17–22.
[61] Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1151–8.
[62] Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. Obesity 2006;14:336–41.
[63] Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Leonetti DL, Newell-Morris L, et al. Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community diabetes study. Diabetes Care 1999;22: 1808–12.
[64] Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004;53:2087–94.
[65] Gozal D, Kheirandish-Gozal L, Serpero LD, Sans Capdevila O, Dayyat E. Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy. Circulation 2007;116:2307–14.
[66] Brunetti L, Francavilla R, Scicchitano P, Tranchino V, Loscialpo M, Gesualdo M, et al. Impact of sleep respiratory disorders on endothelial function in children. ScientificWorldJournal 2013;2013:719456.
[67] Butt M, Khair OA, Dwivedi G, Shantsila A, Shantsila E, Lip GY. Myocardial perfusion by myocardial contrast echocardiography and endothelial dysfunction in obstructive sleep apnea. Hypertension 2011;58:417–24.
[68] Duchna HW, Guilleminault C, Stoohs RA, Faul JL, Moreno H, Hoffman BB, et al. Vascular reactivity in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2000;161:187–91.
[69] Duchna HW, Orth M, Schultze-Werninghaus G, Guilleminault C, Stoohs RA. Long-term effects of nasal continuous positive airway pressure on vasodilatory endothelial function in obstructive sleep apnea syndrome. Sleep Breath 2005;9:97–103.
[70] Duchna HW, Stoohs R, Guilleminault C, Christine Anspach M, Schultze-Werninghaus G, Orth M. Vascular endothelial dysfunction in patients with mild obstructive sleep apnea syndrome. Wien Med Wochenschr 2006;156:596–604.
[71] Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, et al. Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. Circulation 2008;117:2270–8.
[72] Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, et al. Vascular inflammation in obesity and sleep apnea. Circulation 2010;121: 1014–21.
[73] Lattimore JL, Wilcox I, Skilton M, Langenfeld M, Celermajer DS. Treatment of obstructive sleep apnoea leads to improved microvascular endothelial function in the systemic circulation. Thorax 2006;61:491–5.
[74] Patt BT, Jarjoura D, Haddad DN, Sen CK, Roy S, Flavahan NA, et al. Endothelial dysfunction in the microcirculation of patients with obstructive sleep apnea. Am J Respir Crit Care Med 2010;182:1540–5.
[75] Panoutsopoulos A, Kallianos A, Kostopoulos K, Seretis C, Koufogiorga E, Protogerou A, et al. Effect of CPAP treatment on endothelial function and

plasma CRP levels in patients with sleep apnea. Med Sci Monit 2012;18: CR747–51.
*[76] Kohler M, Craig S, Pepperell JC, Nicoll D, Bratton DJ, Nunn AJ, et al. CPAP improves endothelial function in patients with minimally symptomatic OSA: results from a subset study of the MOSAIC trial. Chest 2013;144: 896–902.
[77] Nguyen PK, Katikireddy CK, McConnell MV, Kushida C, Yang PC. Nasal continuous positive airway pressure improves myocardial perfusion reserve and endothelial-dependent vasodilation in patients with obstructive sleep apnea. J Cardiovasc Magn Reson 2010;12:50.
[78] Comondore VR, Cheema R, Fox J, Butt A, John Mancini GB, Fleetham JA, et al. The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. Lung 2009;187:17–22.
*[79] Kohler M, Stoewhas AC, Ayers L, Senn O, Bloch KE, Russi EW, et al. Effects of continuous positive airway pressure therapy withdrawal in patients with obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med 2011;184:1192–9.
[80] Westhoff TH, Schmidt S, Vallbracht-Israng K, Yildirim H, Franke N, Dimeo F, et al. Small artery elasticity assessed by pulse wave analysis is no measure of endothelial dysfunction. J Hypertens 2007;25:571–6.
*[81] Cross MD, Mills NL, Al-Abri M, Riha R, Vennelle M, Mackay TW, et al. Continuous positive airway pressure improves vascular function in obstructive sleep apnoea/hypopnoea syndrome: a randomised controlled trial. Thorax 2008;63:578–83.
[82] Buchner NJ, Quack I, Woznowski M, Stahle C, Wenzel U, Rump LC. Microvascular endothelial dysfunction in obstructive sleep apnea is caused by oxidative stress and improved by continuous positive airway pressure therapy. Respiration 2011;82:409–17.
[83] Trzepizur W, Gagnadoux F, Abraham P, Rousseau P, Meslier N, Saumet JL, et al. Microvascular endothelial function in obstructive sleep apnea: impact of continuous positive airway pressure and mandibular advancement. Sleep Med 2009;10(7):746–52.
[84] Jurado-Gamez B, Fernandez-Marin MC, Gomez-Chaparro JL, Munoz-Cabrera L, Lopez-Barea J, Perez-Jimenez F, et al. Relationship of oxidative stress and endothelial dysfunction in sleep apnoea. Eur Respir J 2011;37:873–9.
[85] Itzhaki S, Lavie L, Pillar G, Tal G, Lavie P. Endothelial dysfunction in obstructive sleep apnea measured by peripheral arterial tone response in the finger to reactive hyperemia. Sleep 2005;28:594–600.
*[86] Seif F, Patel SR, Walia H, Rueschman M, Bhatt DL, Gottlieb DJ, et al. Association between obstructive sleep apnea severity and endothelial dysfunction in an increased background of cardiovascular burden. J Sleep Res 2013;22:443–51.
[87] Kraiczi H, Hedner J, Peker Y, Carlson J. Increased vasoconstrictor sensitivity in obstructive sleep apnea. J Appl Physiol 2000;89:493–8.
[88] Carlson JT, Rangemark C, Hedner JA. Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. J Hypertens 1996;14: 577–84.
[89] Lavie L, Lavie P. Coronary collateral circulation in sleep apnea: a cardioprotective mechanism? Chest 2010;137:511–2.
[90] Imadojemu VA, Gleeson K, Quraishi SA, Kunselman AR, Sinoway LI, Leuenberger UA. Impaired vasodilator responses in obstructive sleep apnea are improved with continuous positive airway pressure therapy. Am J Respir Crit Care Med 2002;165:950–3.
[91] Oyama J, Yamamoto H, Maeda T, Ito A, Node K, Makino N. Continuous positive airway pressure therapy improves vascular dysfunction and decreases oxidative stress in patients with the metabolic syndrome and obstructive sleep apnea syndrome. Clin Cardiol 2012;35:231–6.
[92] Bakker JP, Balachandran JS, Tecilazich F, Deyoung PN, Smales E, Veves A, et al. Pilot study of the effects of bariatric surgery and continuous positive airway pressure treatment on vascular function in obese subjects with obstructive sleep apnoea. Intern Med J 2013;43:993–8.
[93] Shiina K, Tomiyama H, Takata Y, Yoshida M, Kato K, Saruhara H, et al. Effects of CPAP therapy on the sympathovagal balance and arterial stiffness in obstructive sleep apnea. Respir Med 2010;104:911–6.
*[94] Simpson PJ, Hoyos CM, Celermajer D, Liu PY, Ng MK. Effects of continuous positive airway pressure on endothelial function and circulating progenitor cells in obstructive sleep apnoea: a randomised sham-controlled study. Int J Cardiol 2013;168:2042–8.
[95] Shinohara E, Kihara S, Yamashita S, Yamane M, Nishida M, Arai T, et al. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. J Intern Med 1997;241:11–8.
[96] Kritikou I, Basta M, Tappouni R, Pejovic S, Fernandez-Mendoza J, Nazir R, et al. Sleep apnoea and visceral adiposity in middle-aged male and female subjects. Eur Respir J 2013;41:601–9.
[97] Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J Clin Res Ed 1984;288:1401–4.
[98] Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. J Am Coll Cardiol 2013;62:921–5.
[99] Romero-Corral A, Sert-Kuniyoshi FH, Sierra-Johnson J, Orban M, Gami A, Davison D, et al. Modest visceral fat gain causes endothelial dysfunction in healthy humans. J Am Coll Cardiol 2010;56:662–6.
*[100] Hashimoto M, Akishita M, Eto M, Kozaki K, Ako J, Sugimoto N, et al. The impairment of flow-mediated vasodilatation in obese men with visceral fat accumulation. Int J Obes Relat Metab Disord 1998;22:477–84.
[101] Sturm W, Sandhofer A, Engl J, Laimer M, Molnar C, Kaser S, et al. Influence of visceral obesity and liver fat on vascular structure and function in obese subjects. Obes (Silver Spring) 2009;17:1783–8.
[102] Blomster H, Laitinen T, Lyyra-Laitinen T, Vanninen E, Gylling H, Peltonen M, et al. Endothelial function is well preserved in obese patients with mild obstructive sleep apnea. Sleep Breath 2014;18:177–86.
[103] Bruno RM, Rossi L, Fabbrini M, Duranti E, Di Coscio E, Maestri M, et al. Renal vasodilating capacity and endothelial function are impaired in patients with obstructive sleep apnea syndrome and no traditional cardiovascular risk factors. J Hypertens 2013;31:1456–64.
[104] Cassar A, Morgenthaler TI, Rihal CS, Prasad A, Lennon RJ, Lerman LO, et al. Coronary endothelial function in patients with obstructive sleep apnea. Coron Artery Dis 2014;25:16–22.
[105] Chung S, Yoon IY, Shin YK, Lee CH, Kim JW, Lee T, et al. Endothelial dysfunction and C-reactive protein in relation with the severity of obstructive sleep apnea syndrome. Sleep 2007;30:997–1001.
[106] Del Ben M, Fabiani M, Loffredo L, Polimeni L, Carnevale R, Baratta F, et al. Oxidative stress mediated arterial dysfunction in patients with obstructive sleep apnoea and the effect of continuous positive airway pressure treatment. BMC Pulm Med 2012;12:36.
[107] El Solh AA, Akinnusi ME, Baddoura FH, Mankowski CR. Endothelial cell apoptosis in obstructive sleep apnea: a link to endothelial dysfunction. Am J Respir Crit Care Med 2007;175:1186–91.
[108] Jones A, Vennelle M, Connell M, McKillop G, Newby DE, Douglas NJ, et al. Arterial stiffness and endothelial function in obstructive sleep apnoea/hypopnoea syndrome. Sleep Med 2013;14:428–32.
[109] Kohler M, Craig S, Nicoll D, Leeson P, Davies RJ, Stradling JR. Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea. Am J Respir Crit Care Med 2008;178:984–8.
[110] Oflaz H, Cuhadaroglu C, Pamukcu B, Meric M, Ece T, Kasikcioglu E, et al. Endothelial function in patients with obstructive sleep apnea syndrome but without hypertension. Respiration 2006;73:751–6.
[111] Tan HL, Gozal D, Samiei A, Bhattacharjee R, Wang Y, Ramirez HM, et al. T regulatory lymphocytes and endothelial function in pediatric obstructive sleep apnea. PLoS One 2013;8:e69710.
[112] Cereda CW, Tamisier R, Manconi M, Andreotti J, Frangi J, Pifferini V, et al. Endothelial dysfunction and arterial stiffness in ischemic stroke: the role of sleep-disordered breathing. Stroke 2013;44:1175–8.
[113] Kheirandish-Gozal L, Bhattacharjee R, Kim J, Clair HB, Gozal D. Endothelial progenitor cells and vascular dysfunction in children with obstructive sleep apnea. Am J Respir Crit Care Med 2010;182:92–7.
[114] Ohike Y, Kozaki K, Iijima K, Eto M, Kojima T, Ohga E, et al. Amelioration of vascular endothelial dysfunction in obstructive sleep apnea syndrome by nasal continuous positive airway pressure–possible involvement of nitric oxide and asymmetric NG, NG-dimethylarginine. Circ J 2005;69: 221–6.
[115] Tulmac M, Tireli E, Ebinc H, Simsek V, Dogru MT, Yildirim N, et al. Effect of overnight nasal continuous positive airway pressure treatment on the endothelial function in patients with obstructive sleep apnea. Anadolu Kardiyol Derg Anatol J Cardiol 2012;12:560–5.
[116] Jones A, Vennelle M, Connell M, McKillop G, Newby DE, Douglas NJ, et al. The effect of continuous positive airway pressure therapy on arterial stiffness and endothelial function in obstructive sleep apnea: a randomized controlled trial in patients without cardiovascular disease. Sleep Med 2013;14:1260–5.